

### **REMARKS/ARGUMENTS**

Claims 1-14 and 16-17 are pending in the captioned application and stand finally rejected. Applicants respectfully request reconsideration in view of the following arguments.

The claims stand rejected under 35 U.S.C. §103(a) as being unpatentable over Snoke et al. (US 4,055,469) in view of Izumrudov et al. (Biopolymers, Vol. 52, 94-108, 1999). Applicants respectfully disagree.

Applicants submit that Snoke teaches selective precipitation of nucleic acids at high salt concentrations (0.05M phosphate buffer, see Example 6) by polyethyleneimine. However, nothing in Snoke suggests that selective precipitation of nucleic acids (i.e., without precipitating proteins) can be obtained within a broad window of salt concentrations by adding an amount of polycationic agent which provides a charge ratio as claimed in claim 1. This deficiency of Snoke is in fact recognized by the Examiner (see Office action, page 4, first full paragraph).

Applicants further submit that in Snoke, Example 6 is the only reference of selective precipitation of nucleic acids, and uses polyethyleneimine as the precipitating agent. Applicants submit that polyethyleneimine is a mixture of isomers, wherein only the cyclic form contains quaternary amino groups, and the cyclic isomer is present only to a small proportion. See the enclosed article by Spell (Analytical Chemistry, 41, 902-905, 1969), which states in its abstract that as little as 0.2-5% of

polyethyleneimine is the cyclic isomer. Thus, polyethyleneimine could only be "highly charged" at certain pH values.

In comparison, Applicants clearly state in claim 1 that the polycationic precipitating agent is a highly charged linear polymer that comprises quaternary amino groups. This is also supported by the specification, for example, Examples 7 and 8 use polymers with a clearly higher content of quaternary amino groups (poly(N,N'-dimethyldiallylammonium)chloride). Thus, while Applicants claim a method for isolating nucleic acids from other species including proteins by precipitation with a polymer agent comprising quaternary amino groups, nothing in Snoke teaches such.

Applicants note that Snoke states that the amount of polymer added depends on the charge density of the particular polymer and upon the amount of impurities in the extract (column 3, lines 9-11). However, this passage refers to the situation where Snoke suggests to precipitate nucleic acids with protein impurities. Again, Example 6 is the only section with a suggestion to precipitate nucleic acid selectively, without proteins. Here Snoke states first that the salt concentration was the reason why only nucleic acid precipitated and secondly that the 'moderate response' (not totally precipitating the enzyme) was probably due to the low level of precipitating agent. Thus, Example 6 teaches that salt concentration is essential for separating nucleic acids from protein; while the amount of polymer is essential for separating certain proteins (impurities) from others (enzymes). Applicants submit that this in fact teaches away from Applicants' claims, especially with regard to the charge ratio.

Izumrudov teaches that salt concentration is useful in controlling the stability of selectively precipitated nucleic acids (in the form of complexes with polyamines). The only use suggested for such complexes is the transformation of cells (see Introduction), in which case the starting material is very pure DNA preparations. The advantages are that the complex can protect the plasmids from degradation by nucleases, and efficiency in transformation increases. Izumrudov does not teach that nucleic acids can be isolated from proteins using quaternary amino group containing precipitating agents.

Izumrudov teaches that polycations with bulky quaternized amine groups are less stable than if the amines are primary (page 95, the right column, and Abstract: *"Thus, quarternization of a part of the tertiary amine groups of poly(N,N'-dimethylaminoethylmethacrylate) resulted in expected decrease of stability of DNA-containing PECs in water-salt solutions"*). This in fact teaches away from the combination of Snoke with a quaternary amino group containing precipitating agent of Izumrudov for the isolation of nucleic acids. This is because isolation for purification purposes is not suggested in either reference, and one would be expected to use an agent that gives as good stability as possible.

The teachings of Izumrudov about the stability of the complex appear to render the claimed recovery by dissolution of the complex obvious. However, Applicants submit that this is only true with impermissible hindsight with the teaching of the current application. Without the teaching of the current invention, a person skilled in the art reading Izumrudov with the purpose of finding a method for the

purification of nucleic acids will find the need to use a system that provide stable complexes – at least stable enough to allow removal of the other phase. Izumrudov clearly suggests, contrary to Applicants' claims, that primary and secondary amines are better choices.

Applicants submit that neither Snoke nor Izumrudov relates to the selective isolation and purification of desired nucleic acid. As discussed earlier, Snoke does not teach that the precipitating agent used in Example 6 is a highly charged polymer. Further, Snoke teaches away from the idea that the amount of polymer is relevant for the separation of nucleic acids from proteins, and is silent about the charge ratio of polymer/nucleic acid.

Should a skilled person regard Snoke as related to a method for purifying nucleic acids, then to arrive at the currently claimed invention, he needs to supplement Snoke with the feature of quaternary polymers from Izumrudov. The skilled person will learn from Izumrudov that polymer structure and salt concentration are essential to the stability of the complexes formed. However, Izumrudov teaches that complexes formed with quaternary amino group containing polymers are unstable. The skilled person would avoid these polymers and try a different polymer.

Further, the combination is silent about any considerations needed for completing the separation of nucleic acid from proteins (see discussion above with regard to Snoke). In summary, the combination teaches away from one aspect of the claimed invention and is silent about another aspect of claim 1.


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Applicants submit that none of the cited references, whether individually or combined, would render obvious the claimed invention.

Early and favorable consideration is respectfully requested.

Respectfully submitted,

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